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What is Claimed is:

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1. A mutein of human fibroblast growth factor 21 (FGF-21), or a biologically active peptide thereof, comprising the substitution of a charged and/or polar but uncharged amino acid for one or more of the following: glycine 42, glutamine 54, arginine 77, alanine 81, leucine 86, phenylalanine 88, lysine 122, histidine 125, arginine 126, proline 130, arginine 131, leucine 139, alanine 145, leucine 146, isoleucine 152, alanine 154, glutamine 156, glycine 161, serine 163, glycine 170, or serine 172, wherein the numbering of the amino acids is based on SEQ ID NO:1.

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2. The mutein of Claim 1 wherein the negatively charged amino acid is selected from the group consisting of aspartate, glutamate, and non-naturally occurring analogs thereof.

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3. The mutein of Claim 1 wherein the polar but uncharged amino acid is selected from the group consisting of serine, threonine, asparagine, glutamine, and non-naturally occurring analogs thereof.

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4. The mutein of Claim 1, wherein said mutein is selected from the group consisting of Leu139Glu, Ala145Glu, Leu146Glu, Ile152Glu, Gln156Glu, Ser163Glu, Ile152Glu, Ser163Glu, and Gln54Glu.

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5. The mutein of Claim 4 wherein said mutein is truncated at the N-terminus by up to 4 amino acids.

6. A polynucleotide encoding the mutein of Claim 1.

7. The polynucleotide of Claim 6, wherein said polynucleotide is DNA.

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8. An expression vector containing the DNA of Claim 7.

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9. A host cell comprising the expression vector of Claim 8.

10. The host cell of Claim 9 wherein said host cell is a yeast cell.

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11. A process for producing a polypeptide comprising:

- (a) expressing said polypeptide from the host cell of Claim 10, and;
- (b) isolating said polypeptide.

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12. A pharmaceutical composition comprising a therapeutically effective amount of the FGF-21 mutein of Claim 1 and an acceptable pharmaceutical carrier, wherein said composition is useful for treating a patient exhibiting one or more of the indications from the group consisting of obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome

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13. A method for treating a patient comprising administering to said patient a therapeutically effective amount of the FGF-21 mutein of Claim 1, wherein said patient exhibits one or more of the indications from the group consisting of obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome.

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14. The method of Claim 13 wherein said patient exhibits type 2 diabetes.

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15. A mutein of human FGF-21, or a biologically active peptide thereof, comprising the substitution of a cysteine for two or more of the following: arginine 19, tyrosine 20, leucine 21, tyrosine 22, threonine 23, aspartate 24, aspartate 25, alanine 26, glutamine 27, glutamine 28, alanine 31, leucine 33, isoleucine 35, leucine 37, valine 41, glycine 42, glycine 43, glutamate 50, glutamine 54, leucine 58, valine 62, leucine 66, glycine 67, lysine 69, arginine 72, phenylalanine 73, glutamine 76, arginine 77, aspartate 79, glycine 80, alanine 81, leucine 82, glycine 84, serine 85, proline 90, alanine 92, serine 94, phenylalanine 95, leucine 100, aspartate 102, tyrosine 104, tyrosine 107, serine 109, glutamate 110, proline 115, histidine 117, leucine 118, proline 119, asparagine 121, lysine

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5 122, serine 123, proline 124, histidine 125, arginine 126, aspartate 127, alanine 129, proline 130, glycine 132, alanine 134, arginine 135, leucine 137, proline 138, or leucine 139, wherein the numbering of amino acids is based on SEQ ID NO:1.

10 16. The mutein of Claim 15, wherein said mutein is selected from the group consisting of Leu21Cys-Leu33Cys/Leu118Cys-Ala134Cys, Leu21Cys/Leu33Cys, Leu118Cys/Ala134Cys, or Ala26Cys/Lys122Cys.

15 17. The mutein of Claim 16 wherein said mutein is truncated at the N-terminus by up to 4 amino acids.

18. The mutein of Claim 17 wherein said mutein is *des*-HPIP-Leu118Cys/Ala134Cys.

20 19. A polynucleotide encoding the mutein of Claim 15.

20. The polynucleotide of Claim 19, wherein said polynucleotide is DNA.

21. An expression vector containing the DNA of Claim 20.

25 22. A host cell comprising the expression vector of Claim 21.

23. The host cell of Claim 22 wherein said host cell is a yeast cell.

24. A process for producing a polypeptide comprising:

- 30 (a) expressing said polypeptide from the host cell of Claim 23, and;
(b) isolating said polypeptide.

25. A pharmaceutical composition comprising a therapeutically effective amount of the FGF-21 mutein of Claim 15 and an acceptable pharmaceutical carrier, wherein said
35 composition is useful for treating a patient exhibiting one or more of the indications from

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5 the group consisting of obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome.

26. A method for treating a patient comprising administering to said patient a therapeutically effective amount of the FGF-21 mutein of Claim 15, wherein said patient
10 exhibits one or more of the indications from the group consisting of obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome.

27. The method of Claim 26 wherein said patient exhibits type 2 diabetes.
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28. A mutein of human FGF-21, or a biologically active peptide thereof, comprising the substitution of a charged and/or polar but uncharged amino acid for one or more of the amino acids at positions: glycine 42, glutamine 54, arginine 77, alanine 81, leucine 86, phenylalanine 88, lysine 122, histidine 125, arginine 126, proline 130, arginine 131, leucine 139, alanine 145, leucine 146, isoleucine 152; alanine 154; glutamine
20 156, glycine 161, serine 163, glycine 170, or serine 172; in combination with the substitution of a cysteine for two or more of the amino acid at positions: arginine 19, tyrosine 20, leucine 21, tyrosine 22, threonine 23, aspartate 24, aspartate 25, alanine 26, glutamine 27, leucine 28, alanine 31, leucine 33, isoleucine 35, leucine 37, valine 41, glycine 42, glycine 43, glutamate 50, glutamine 54, leucine 58, valine 62, leucine 66,
25 glycine 67, lysine 69, arginine 72, phenylalanine 73, glutamine 76, arginine 77, aspartate 79, glycine 80, alanine 81, leucine 82, glycine 84, serine 85, proline 90, alanine 92, serine 94, phenylalanine 95, leucine 100, aspartate 102, tyrosine 104, tyrosine 107, serine 109, glutamate 110, proline 115, histidine 117, leucine 118, proline 119, asparagine 121, lysine
30 122, serine 123, proline 124, histidine 125, arginine 126, aspartate 127, alanine 129, proline 130, glycine 132, alanine 134, arginine 135, leucine 137, proline 138, or leucine 139, wherein the numbering of amino acids is based on SEQ ID NO:1.

29. A polynucleotide encoding the mutein of Claim 28.
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30. The polynucleotide of Claim 29, wherein said polynucleotide is DNA.

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31. An expression vector containing the DNA of Claim 30.

32. A host cell comprising the expression vector of Claim 31.

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33. The host cell of Claim 32 wherein said host cell is a yeast cell.

34. A process for producing a polypeptide comprising:

- (a) expressing said polypeptide from the host cell of Claim 33, and;
- (b) isolating said polypeptide.

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35. A pharmaceutical composition comprising a therapeutically effective amount of the FGF-21 mutein of Claim 28 and an acceptable pharmaceutical carrier, wherein said composition is useful for treating a patient exhibiting one or more of the indications from the group consisting of obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome.

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36. A method for treating a patient comprising administering to said patient a therapeutically effective amount of the FGF-21 mutein of Claim 28, wherein said patient exhibits one or more of the indications from the group consisting of obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome.

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37. The method of Claim 36 wherein said patient exhibits type 2 diabetes.

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38. The mutein of Claim 28 wherein said mutein is truncated at the N-terminus by up to 4 amino acids.

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39. The use of the FGF-21 mutein of Claim 1 for the manufacture of a medicament for the treatment of one or more of the indications from the group consisting of obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome.

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5 40. The use of the FGF-21 mutein of Claim 15 for the manufacture of a
medicament for the treatment of one or more of the indications from the group consisting
of obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance,
hyperglycemia, or metabolic syndrome.

10 41. The use of the FGF-21 mutein of Claim 28 for the manufacture of a
medicament for the treatment of one or more of the indications from the group consisting
of obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance,
hyperglycemia, or metabolic syndrome.

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